ANALGESIA METHOD

FIELD OF THE INVENTION

The present invention relates generally to methods of reducing opioid tolerance in patients undergoing treatment with an opioid analgesic who have become tolerant to the opioid as a result of its prolonged administration. In particular, such patients are administered compositions as shown in formula (I) in order to reduce their opioid tolerance. The present invention also relates to compositions and kits useful for the reduction of opioid tolerance in a patient.

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is a U.S. national phase filing under 35 U.S.C. 371 of PCT application No. PCT/GB 2004/004389, filed October 14, 2004, which claims the benefit of United Kingdom Patent Application No: 0324423.3, filed October 18, 2003 each of which are hereby incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

Opioid analgesics, principally morphine and its derivatives, are the drugs of choice for the treatment of patients suffering severe chronic pain. Unfortunately, repeated dosing leads to tolerance and therefore reduced effectiveness of opioid analgesics. This, in turn, results in increasing doses of the opioid being administered, with consequential undesirable side effects. It would therefore be desirable if opioid tolerance could be reduced or prevented and a patient's level of analgesic relief restored. Hence, there is a pressing need for a method of reducing opioid tolerance in a patient receiving opioids for a prolonged period of time.

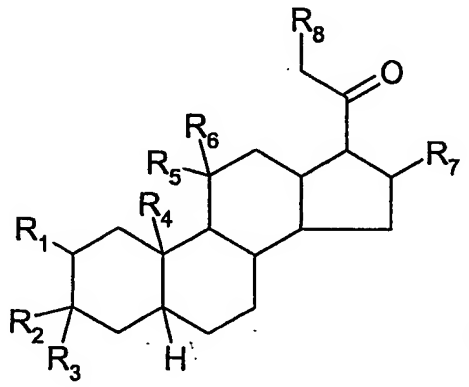
SUMMARY OF THE INVENTION

US patent 6,048,848 ("the '848 patent") discloses the use of members of a class of pregnane-dione neurosteroids as non-sedating analgesics. Alphadolone (21-acetoxy-3-alpha- hydroxy-5-alpha-pregnane-11, 20-dione), for example, is identified as an exemplary member of the class. According to this patent, this class of compounds "may be used concurrently with other analgesic drugs to potentiate or increase the analgesic effects of those drugs" and morphine is cited as an example of one such drug suitable for concurrent administration.

Unexpectedly, it was found that the class of neurosteroids disclosed in the '848 patent may also be administered to opioid-tolerant patients to reduce that tolerance and, therefore, restore the analgesic effectiveness of the opioid in those patients. This effect is not predictable from the disclosure in the '848 patent and was a surprising result. This is a valuable effect, since it allows the continuation of treatment with the opioid, (often the drug of choice for such patients), and restoration of its effectiveness at lower, safer doses.

Accordingly, in one embodiment of the present invention there is provided a method for reducing opioid tolerance in a patient undergoing treatment with that opioid after he or she has become tolerant to the opioid as a result of that treatment, by treating the patient with a composition of formula (I)

In one embodiment, a method for reducing opioid tolerance in a patient undergoing treatment with that opioid who has become tolerant thereto as a result of that treatment is provided whereby the patient is administered an effective amount of a compound of formula (I)



(I)

wherein

R1 is selected from the group consisting of H and methyl;

R2 is OH;

R3 is H;

or R2 and R3 taken together are O;

R4 is selected from the group consisting of H and methyl;

R5 and R6 are each H;

or R5 and R6 taken together are O;

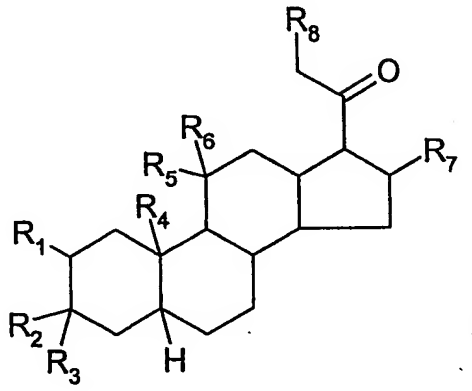
R7 is selected from the group consisting of H and methyl;

R8 is selected from the group consisting of H, OH,-OC (=O) CH3, SH,-SC (=O) CH3, Cl, Br and F;

or a pharmaceutically acceptable derivative thereof;

and the compound of formula (I) is administered either (i) while the patient is also undergoing treatment with said opioid or (ii) after cessation of treatment with said opioid and prior to resumption of treatment with said opioid.

In another embodiment, a composition for reducing opioid tolerance in a patient undergoing treatment with that opioid who has become tolerant thereto as a result of that treatment is provided, whereby a patient is administered a compound of formula (I)



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R5 and R6 are each H;

or R5 and R6 taken together are O;

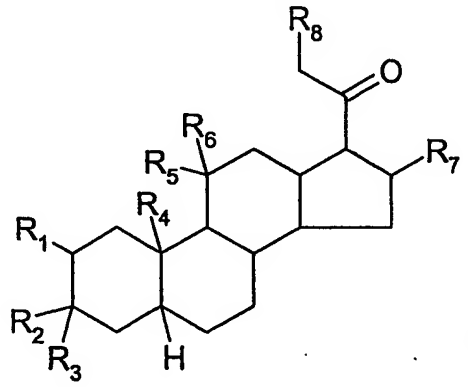
R7 is selected from the group consisting of H and methyl;

R8 is selected from the group consisting of H, OH,-OC (=O) CH3, SH,-SC (=O) CH3, Cl, Br and F;

or a pharmaceutically acceptable derivative thereof;

and the compound of formula (I) is for administration either (i) while the patient is also undergoing treatment with said opioid or (ii) after cessation of treatment with said opioid and prior to resumption of treatment with said opioid.

In another embodiment, a kit is provided for reducing opioid tolerance in a patient undergoing treatment with that opioid who has become tolerant thereto as a result of that treatment, whereby an effective amount of a compound of formula (I)



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or R5 and R6 taken together are O;

R7 is selected from the group consisting of H and methyl;

R8 is selected from the group consisting of H, OH,-OC (=O) CH3, SH,-SC (=O) CH3, Cl, Br and F;

or a pharmaceutically acceptable derivative thereof; and

instructions for administration of said compound of formula (I) either (i) while the patient is also undergoing treatment with said opioid or (ii) after cessation of treatment with said opioid and prior to resumption of treatment with said opioid is provided in the kit.

In one embodiment the compound of formula (I) is used in a form selected from the group consisting of a solvate, salt, prodrug, and analgesically active metabolite thereof.

In another embodiment, R1 is H.

In yet another embodiment, R2 and R4 are in the alpha conformation.

In a particular embodiment, the compound of formula (I) may be selected from the group consisting of 21-acetoxy-3-alpha-hydroxy-5-alpha-pregnane-11, 20-dione, 3-alpha-hydroxy-5-beta- pregnane-20-one and 3-alpha-hydroxy-5-alpha- pregnane-20-one. 21-acetoxy-3-alpha-hydroxy-5-alpha-pregnane-11, 20-dione, in particular, may be administered as its acetate or glucuronide.

Any opiod may be utilized with the methods, compositions and kits of the present invention. In a particular embodiment, the opoid is selected from the group consisting of morphine, fentanyl, oxycodone, codeine, dihydrocodeine, dihydrocodeinone enol acetate, desomorphine, apomorphine, pethidine, methadone, dextropropoxyphene, pentazocine, dextromoramide, oxymorphone, hydromorphone, dihydromorphine, noscapine, papaverine, papaveretum, alfentanil, buprenorphine, tramadol and pharmaceutically acceptable derivatives thereof.

The opiods of the present invention may be administered in any manner considered effective for a particular purpose. In a particular embodiment, such manner of administration is selected from

the group consisting of intravenously, intramuscularly, intraperiotoneally, intragastrically, intestinally, transdermally or intrathecally.

The compound of formula (I) of the present invention may be administered in any pharmaceutical formulation considered effective for a particular purpose. In a particular embodiment, it is administered in an orally administrable pharmaceutical formulation.

Compounds of formula (I) may be used in any convenient solvate-, salt-, tautomeric-, analgesically active metabolite, or prodrug form thereof. Salt forms include, but are not limited to, the acetate, sulphate, and methane sulphonate forms. Analgesically active metabolite forms of the compounds (I) include, but are not limited to, the glucuronide.

Additional advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DETAILED DESCRIPTION OF THE INVENTION

The present invention may be understood more readily by reference to the following detailed description of particular embodiments of the invention and the Examples included therein.

Before the present compounds, compositions, and/or methods are disclosed and described, it is to be understood that this invention is not limited to specific synthetic methods, specific reagents or to laboratory or manufacturing techniques, as such may, of course, vary, unless it is otherwise indicated. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

BRIEF DESCRIPTION OF THE FIGURES

The present invention will be further described with reference to the following figures.

Figure 1 illustrates the nociceptive thresholds assessed with the ECT test for 44 hours after 250-mg/kg alphadolone administered in a slow release emulsion according to an embodiment of the present invention. Points illustrate means and bars SEM (n = 10). The nociceptive threshold appeared to be significantly increased by the one-hour reading and remained elevated for approximately 24 hours.

Figure 2 illustrates the results of the rotarod test in rats that received subcutaneous injections of emulsions of alphadolone (250 mg/kg; n = 9)) and alphaxalone (80 mg/kg ; n = 9) given at time zero on two successive days according to an embodiment of the present invention. Alphadolone appeared to cause a small but significant amount of sedation (run time less than normal value of 120s) at 1 hour after the injection (* $p < 0.05$) but no apparent sedation after that. By contrast alphaxalone appeared to cause significant sedative effects for approximately four hours and this sedation appeared significantly greater than that caused by alphadolone in the first hour (* $p < 0.01$)

Figure 3 illustrates the results of the tail flick latency test in response to 6.4 mg/kg ip morphine in rats before and after they had received two day treatment with subcutaneous morphine emulsion injections in combination with subcutaneous sustained release emulsions containing alphadolone (250 mg/kg/day) or alphaxalone (80 mg/kg/day) compared with Cremophor/saline vehicle according to an embodiment of the present invention. Histograms illustrate means and bars SEM. Significant tolerance appeared to occur to the same extent in the vehicle and alphaxalone treated groups (* $p = 0.0804$) whereas the tolerance that occurred in the alphadolone treated rats appeared less than that in saline treated controls ($p = 0.0101$, Students t test.)

Figure 4 illustrates TFL responses to intraperitoneal morphine (6.25 mg/kg aqueous immediate release formulation) in rats before (pre tolerance) and after (post tolerance) two days of treatment with subcutaneous morphine sustained release emulsion according to an embodiment of the present invention. Intraperitoneal injection of immediate release morphine (6.4 mg/kg) on day 1 in both groups appeared to cause similar tail flick latency responses (approximately 80% MPE). Significant tolerance appeared to occur after the two day treatment with morphine emulsion as observed on day 3 in the saline treated group (shaded histogram, $p<0.01$ one way ANOVA with Tukey post hoc test). By contrast the response to that same dose of morphine on day 3, when co-

administered with alphadolone 10 mg/kg, appeared to be the same as that produced on day 1 before the treatment with morphine emulsion to cause tolerance ($p > 0.05$, one way ANOVA). Histograms illustrate means and bars SEM ($n = 9$).

Definitions

For the purpose of the present invention, the following terms shall have the following meanings:

For the purpose of the present invention, the term, "compound of formula (I)" is to be understood to mean any or all members of the class of compounds with the characteristics recited in the specification and claims for a compound of formula (I). One exemplary member of this class are neurosteroids.

As used herein, opioid compounds (opioids) include any compound which is a partial or full agonist of an opioid receptor.

Moreover, for the purpose of the present invention, the term "a" or "an" entity refers to one or more of that entity; for example, "a compound of formula I" or "an " refers to one or more of those compounds or at least one compound. As such, the terms "a" (or "an"), "one or more" and "at least one" can be used interchangeably herein. It is also to be noted that the terms "comprising", "including", and "having" can be used interchangeably. Furthermore, a compound "selected from the group consisting of" refers to one or more of the compounds in the list that follows, including mixtures (i.e. combinations) of two or more of the compounds. According to the present invention, an isolated, or biologically pure, protein or nucleic acid molecule is a compound that has been removed from its natural millieu. As such, "isolated" and "biologically pure" do not necessarily reflect the extent to which the compound has been purified. An isolated compound of the present invention can be obtained from a natural source, can be produced using molecular biology techniques or can be produced by chemical synthesis.

Finally, for the purposes of the present invention, the term "patient" means an animal or human of either gender.

Reference will now be made in detail to particular embodiments of the invention.

The methods of the present invention include the administration of compounds of formula (I) to an opioid tolerant patient while he or she is also undergoing treatment with that opioid. The compositions of the present invention include compositions of formula (I) for administration to opioid tolerant patients. The kits of the present invention provide compounds of formula (I) and instructions for the administration of the same to opioid tolerant patients. In the methods, compositions and kits of the present invention, the compounds of formula (I) may be administered with doses of the opioid, or alternating doses of compounds of formula (I) and opioid may be administered. Alternatively, treatment of the patient with opioid may be stopped, and a period of dosing with the compounds of formula (I) commenced, during which time opioid sensitivity is restored. Since the compound of formula (I) has analgesic activity in its own right, cessation of the opioid treatment should not cause the patient excessive discomfort as a result of his or her on-going pain condition.

If opioid sensitivity returns in a patient, dosing with the opioid may be resumed, either with or without co-treatment with the compound of formula (I). In the latter case however, it is to be expected that opioid tolerance will return, and the method of the invention may then be applied again to reduce that tolerance.

In one embodiment, a method for reducing opioid tolerance in a patient undergoing treatment with that opioid who has become tolerant thereto as a result of that treatment is provided whereby the patient is administered an effective amount of a compound of formula (I) and the compound of formula (I) is administered either (i) while the patient is also undergoing treatment with said opioid or (ii) after cessation of treatment with said opioid and prior to resumption of treatment with the opioid.

In a second embodiment, a composition for reducing opioid tolerance in a patient undergoing treatment with that opioid who has become tolerant thereto as a result of that treatment is provided, whereby a patient is administered a compound of formula (I) for either (i) while the patient is also undergoing treatment with said opioid or (ii) after cessation of treatment with said opioid and prior to resumption of treatment with said opioid.

In a third embodiment, a kit is provided for reducing opioid tolerance in a patient undergoing treatment with that opioid who has become tolerant thereto as a result of that treatment, whereby an effective amount of a compound of formula (I) and instructions for administration of said compound of formula (I) is provided for administration for either (i) while the patient is also undergoing treatment with said opioid or (ii) after cessation of treatment with said opioid and prior to resumption of treatment with said opioid.

Dosage with the compound of formula (I) may be by any convenient route, utilizing appropriate formulations. Thus, it may be formulated for intragastric (especially oral), subcutaneous, intramuscular, intraperiotoneal, intrathecal, intestinal, intravenous, or transdermal administration. An advantage of the present invention lies in the fact that administration of tolerance-reducing analgesic doses of the composition of formula (I), such as alphadolone, by routes other than intravenous does not result in overt sedation. Hence, in a particular embodiment, administration is via non-intravenous routes, such as by oral administration. In a particular embodiment, administration is in the form of tablets or capsules, or in liquid form as solutions, suspensions or syrups.

Thus, the compounds of formula I may be in crystalline form, either as the free compounds or as solvates (e.g. hydrates). Methods of salvation are generally known within the art.

In one embodiment the compound of formula (I) is used in a form selected from the group consisting of a solvate, salt, prodrug, and analgesically active metabolite thereof.

In another embodiment, R1 is H.

In yet another embodiment, R2 and R4 are in the alpha conformation.

In a particular embodiment, the compound of formula (I) may be selected from the group consisting of 21-acetoxy-3-alpha-hydroxy-5-alpha-pregnane-11, 20-dione, 3-alpha-hydroxy-5-beta- pregnane-20-one and 3-alpha-hydroxy-5-alpha- pregnane-20-one. 21-acetoxy-3-alpha-hydroxy-5-alpha-pregnane-11, 20-dione, in particular, may be administered as its acetate or glucuronide.

Any opiod may be utilized with the methods, compositions and kits of the present invention. In a particular embodiment, the opoid is selected from the group consisting of morphine, fentanyl, oxycodone, codeine, dihydrocodeine, dihydrocodeinone enol acetate, desomorphine, apomorphine, pethidine, methadone, dextropropoxyphene, pentazocine, dextromoramide, oxymorphone, hydromorphone, dihydromorphine, noscapine, papaverine, papaveretum, alfentanil, buprenorphine, tramadol and pharmaceutically acceptable derivatives thereof.

The opiods of the present invention may be administered in any manner considered effective for a particular purpose. In a particular embodiment, such manner of administration is selected from the group consisting of intravenously, intramuscularly, intraperiotoneally, intragastrically, intestinally, transdermally or intrathecally.

The compound of formula (I) of the present invention may be administered in any pharmaceutical formulation considered effective for a particular purpose. In a particular embodiment, it is administered in an orally administrable pharmaceutical formulation.

Compounds of formula (I) may be used in any convenient solvate-, salt-, tautomeric-, analgesically active metabolite, or prodrug form thereof. Salt forms include, but are not limited to, the acetate, sulphate, and methane sulphonate forms. Analgesically active metabolite forms of the compounds (I) include, but are not limited to, the glucuronide.

EXAMPLES

The following examples are included to demonstrate particular embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventors to function well in the practice of the invention, and thus can be considered to merely constitute particular modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

In the following examples, alphadolone acetate is used as a representative member of the compositions of formula (I) with which the invention is concerned. Alphaxalone, a steroid which is not a member of the class of compositions of formula (I) with which this invention is concerned, and which is known to produce sedation, is used as a comparison compound. Morphine is used as a representative opioid to which patients are known to grow tolerant during long term treatment.

This work was carried out with permission of the Monash University Standing Committee on Ethics in Animal Experimentation. In all experiments attention was paid to ethical guidelines for the investigation of experimental pain in conscious animals.

Animal Care:

Rats were housed singly with a 12h light/dark cycle with free access to food and water.

Production of Compositions of Formula (I) and Induction of Tolerance:

The method of formulating morphine in a slow release emulsion is well known in the art. Briefly, an aqueous solution of morphine sulphate (David Bull Laboratories, Mulgrave, Australia) was mixed with liquid paraffin and mannide mono-oleate and then stirred to form an emulsion. This method lead to the production of a sustained release formulation capable of releasing morphine from a subcutaneous depot over a 24 hr period with no morphine left at the subcutaneous injection site after 24 hours.

Nine rats were then given 1.0 ml subcutaneous injections of the morphine emulsion to induce morphine tolerance. The rats were dosed on day one with 62.5 mg/kg morphine in an emulsion formulation in both the morning and afternoon. The dose was then increased to 125 mg/kg in the morning of day two.

Emulsions containing alphadolone acetate (Jurox, Newcastle, Australia), alphaxalone (Jurox, Newcastle, Australia) or saline (placebo control) were also prepared. Alphaxalone was used as an active comparator since it is a neurosteroid anaesthetic very similar in structure to alphadolone but three times more potent as an anaesthetic but without antinociceptive properties.

The emulsion was prepared in such a way that the composition of formula (I) would be released with the same time profile as had been observed with the morphine emulsion. This was tested for alphadolone by measurement of antinociceptive effects as illustrated below.

Briefly, Alphadolone acetate 400mg was dispersed in 13. 6ml 20% Cremophor EL. Saline solution (3ml) was then added to 11 ml of the alphadolone/Cremophor mix prior to the addition of 8ml liquid paraffin. Emulsifier (mannide mono oleate ; 1 ml) was then added to the mixture, which was stirred to produce a homogeneous emulsion. Similar emulsions were made containing vehicle only (20% Cremophor EL) and alphaxalone (133mg).

Characterization of Sustained Release Profile of Alphadolone Emulsion:

Ten rats (wt 150-180g) were placed in a restrainer and the nociceptive threshold was measured in the tail using the electrical current threshold test (ECT) as previously described (Edwards, Serrao et al. 1990; Serrao, Stubbs et al. 1989). Briefly, pairs of electrical stimulating electrodes were placed on the skin surface of the tail and electrical current was passed through the electrodes (50 Hz, 1 ms pulses, 0.5 s train) to determine the minimum current necessary to cause the rat to squeak or make a strong aversive movement as defined by the up-down method. The ECT value was taken as the mean of three consecutive readings taken at 5-minute intervals after a stable baseline had been reached. The rats were then released and a subcutaneous injection of alphadolone emulsion (250mg/kg alphadolone acetate) was administered. They were then returned to the restrainer for further ECT measurements at 1, 3, 6, 21, 24, 27 and 44 hours after the alphadolone injection.

Comparison of the Sedative Effects of Alphadolone and Alphaxalone Sustained Release Emulsions:

Sixteen male Wistar rats (wt 180-200g) were divided into two equal groups and each rat was subjected to the rotarod running test to assess sedation. The rats were naïve to the drugs with no previous exposure to the rotarod test.

After an initial assessment, they were placed on the rotarod accelerator treadmill (7650 accelerator rotarod, Ugo Basile, Italy) set at the minimum speed for two training sessions of 1-2 minutes separated by an interval of 30-60 minutes. After this conditioning period, the rotarod running time was tested before the neurosteroid injection and at one-hour intervals thereafter for eight hours.

Each rat received a 1.0 ml subcutaneous injection of either alphadolone (250 mg/kg) or alphaxalone (80 mg/kg) subcutaneously in a sustained release emulsion in an observer-blinded manner. At each testing time the rats were placed individually onto the rotarod set at a constant speed of 4 revolutions per minute. As the animal took grip of the drum the accelerator mode was selected on the treadmill, i. e. the rotation rate of the drum was increased linearly at the rate of 20 revolutions per minute every minute thereafter. The time was measured from the start of the acceleration period until the rat fell off the drum. A cut-off or maximum runtime for the test was 2 minutes because normal non-sedated rats all ran for 2 minutes at which time the test was terminated. The runtime values were combined for each drug and testing time to calculate means SEM. This process was repeated on the following day to mirror the protocol for administration of the neurosteroids in combination with morphine emulsion to test for their effects on tolerance as described below.

Effect of Sustained Release Alphadolone On The Development of Morphine Tolerance:

Male Wistar rats (wt 180-200g) were treated with morphine sustained release emulsion to cause morphine tolerance as described above. They were then divided randomly into two groups. In addition to the treatment with morphine emulsion, group 1 (n = 27) received a 1.0 ml subcutaneous injection of emulsion vehicle with no drug added, group 2 (n = 13) received a subcutaneous injection of alphadolone emulsion (250 mg/kg alphadolone acetate) and group 3 (n

= 15) received a subcutaneous injection of alphaxalone emulsion (80 mg/kg alphaxalone). These extra subcutaneous injections were given in the mornings of day one and day two at the same time as the morphine injections. These injections were given such that the observer making the measurements of antinociceptive effects was unaware as to the nature of the treatment that each rat had received. Shuffling a set of unlabelled envelopes containing the details of each rat and the allocated treatment randomised the treatments.

At the beginning of day one prior to subcutaneous injections, and in the morning of day three after the treatment with morphine and alphadolone as described above, each rat was placed in a restrainer. Nociceptive thresholds were measured in the tail every five minutes using tail flick latency (TFL) as described previously (Edwards, Serrao, Gent, and Goodchild 1990; Serrao, Stubbs, Goodchild, and Gent 1989). After three stable control pre-drug injection readings had been obtained, an immediate release aqueous solution of morphine sulphate (6.4 mg/kg; David Bull Laboratories, Mulgrave, Victoria, Australia) was injected intraperitoneally and measurements of nociceptive thresholds were continued every five minutes for 25 minutes. The antinociceptive effects were calculated as percentage maximum possible effect (% MPE) for tail flick as described previously. In this way the presence or absence of tolerance to morphine could be shown in the three groups by comparison of the responses to intraperitoneal morphine on day one (pre-treatment) with the responses to the same dose on day three after the morphine emulsion treatment (post-treatment).

Effect of Alphadolone On Established Morphine Tolerance:

Two groups of rats (wt 150-299g; n = 9 each group) were treated as follows in a randomized placebo controlled fashion. On day one TFL response was measured in each rat to an intraperitoneal injection of an immediate release aqueous solution of morphine 6.4mg/kg. All rats were then made tolerant to morphine by subcutaneous morphine emulsion injections for two days as described above. On the third day TFL responses were measured in response to a further intraperitoneal aqueous morphine sulphate injection (6.4 mg/kg) given in combination with either 1.0 ml saline or a 1.0 ml saline suspension containing alphadolone 10 mg/kg. An observer unaware of the nature of this treatment, saline or alphadolone, then made the TFL measurements.

The TFL responses on day 1 and day 3 were combined for drug treatment and expressed as means SEM. These values were then compared to see if tolerance occurred and whether co-administration of alphadolone caused reversal of the tolerance effect.

Statistics:

Replicate values for drug and time of measurement were combined and expressed graphically as means SEM. Comparisons between treatments were made with one-way ANOVA with a Tukey post hoc test. A value of $p < 0.05$ was regarded as statistically and biologically significant.

Results:

Characterization of Sustained Release Profile of Alphadolone Emulsion:

The alphadolone injections did not cause any rat to lose consciousness or in any way to look sedated. Figure 1 shows the nociceptive thresholds assessed with the ECT test for 44 hours after 250-mg/kg alphadolone administered in the slow release emulsion. Points show means and bars SEM (n = 10). The nociceptive threshold was significantly increased by the one-hour reading and remained elevated for 24 hours. Thus, the emulsion appears to have slowly released the alphadolone to extend the activity for a continuous 24- hour period. Therefore, the alphadolone administered in this emulsion appears to be present in the rat with a time profile similar to that published for the morphine emulsion (Salem and Hope 1998).

Comparison of the Sedative Effects of Alphadolone and Alphaxalone Sustained Release Emulsions:

Figure 2 illustrates the results of the rotarod test in rats that received subcutaneous injections of emulsions of alphadolone (250 mg/kg; n = 9)) and alphaxalone (80 mg/kg; n = 9) given at time zero on two successive days according to an embodiment of the present invention.

Alphadolone appeared to cause a small but significant amount of sedation at 1 hour after the injection ($p < 0.05$) but no sedation after the initial one hour. In contrast, alphaxalone appeared to cause a significant sedative effects for four hours and this sedation was significantly greater than that caused by alphadolone in the first hour ($p < 0.01$).

Effect of Sustained Release Alphadolone On The Development of Morphine Tolerance:

Figure 3 illustrates the results of the tail flick latency test in response to 6.4 mg/kg intraperitoneal morphine on days one and three in those rats that received subcutaneous morphine emulsion injections in combination with subcutaneous sustained release emulsions containing alphadolone or alphaxalone compared with Cremophor/saline vehicle. The pre treatment TFL responses to 6.4 mg intraperitoneal immediate release morphine appeared to be similar for all three groups ($p > 0.05$).

Significant tolerance to morphine did appear to occur in the vehicle treated group ($p < 0.001$, one way ANOVA). Although there was tolerance in the alphadolone treated group, there was a statistically significant difference between the post treatment TFL values in the saline and alphadolone treated animals ($p = 0.0101$, Students t test). By contrast, significant tolerance appeared to occur in the alphaxalone treated rats and the post treatment values in this group did not differ from those in vehicle treated controls ($p > 0.05$, Students t test).

Furthermore those rats treated with alphaxalone appeared heavily sedated during the whole course of this experiment whereas the rats treated with alphadolone showed no overt signs of sedation.

Effect of Alphadolone On Established Morphine Tolerance:

Figure 4 illustrates the results of the series of experiments in which all rats received subcutaneous morphine emulsion in order to cause morphine tolerance according to an embodiment of the present invention.

Intraperitoneal injection of immediate release morphine (6.4 mg/kg) on day 1 in both groups appeared to cause similar tail flick latency responses (approximately 80% MPE). Significant tolerance appeared to occur after the two day treatment with morphine emulsion as indicated on day 3 in the saline treated group; 6.4 mg/kg immediate release morphine given intraperitoneally on day 3 in combination with saline caused only 29 8 % MPE rise in TFL ($p < 0.01$) when compared with pre-tolerance levels ; (one way ANOVA with Tukey post hoc test). In contrast, the response to that same dose of morphine on day 3, when co administered with alphadolone 10

mg/kg appeared to be 78.6 9.8 % MPE (mean SEM) equal to that produced on day 1 before the treatment with morphine emulsion to cause tolerance ($p > 0.05$, one way ANOVA).

Remarks:

It appears from the experiments above, that in addition to preventing the development of tolerance to morphine when it is given at the same time as the morphine, alphadolone may also reverse the effects of established tolerance. Hence, alphadolone may have clinical utility as an analgesic used to enhance the antinociceptive effects of opioids by virtue of its ability to potentiate them. Therefore this result may have important clinical implications in maintaining analgesic effectiveness in long-term therapy.

All of the COMPOSITIONS, METHODS and KITS disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of particular embodiments, it will be apparent to those of skill in the art that variations may be applied to the COMPOSITIONS, METHODS and KITS and in the steps or in the sequence of steps of the methods described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents that are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

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The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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Citation of the above documents is not intended as an admission that any of the foregoing is prior art. All statements as to the date or representation as to the content of these documents is based on subjective characterization of information available to the applicant, and does not constitute any admission as to the accuracy of the dates or contents of the documents.

ABSTRACT

The present invention relates to methods of reducing opioid tolerance in patients undergoing treatment with an opioid analgesic who have become tolerant to the opioid as a result of its prolonged administration. In particular, such patients are administered compositions as shown in formula (I) in order to reduce their opioid tolerance. The present invention also relates to compositions and kits useful for the reduction of opioid tolerance in a patient.

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/GB2004/004389

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/57 A61K31/573 A61K31/485 A61P25/04 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 048 848 A (GOODCHILD COLIN STANLEY ET AL) 11 April 2000 (2000-04-11) cited in the application the whole document	1-11
X	WO 03/018027 A (GOODCHILD COLIN STANLEY ; UNIV MONASH (AU); NADESON RAYMOND (AU)) 6 March 2003 (2003-03-06) the whole document	1-11
X	WO 97/07807 A (GOODCHILD COLIN STANLEY) 6 March 1997 (1997-03-06) the whole document	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

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